REMARKS

Interview Summary

The Applicant's representative thanks the Examiner for the courtesies extended in a telephonic interview following issuance of a Final Office Action. The interview was held on December 1. During the interview, the dominant negative ATF2 described in the cited prior art references (van Dam and US 6,579,856) was discussed. The Applicant's representative pointed out that this dominant negative was a mutated ATF2 wherein amino acid residues 69 and 71 were replaced with alanine residues, precluding phosphorylation, and hence, transactivation by ATF2. This dominant negative is distinct from the non-mutated ATF2 fragment (50-100) of the claims (as amended), which is derived from the wild-type sequence. This is discussed further below.

Also discussed during the interview was the possibility of amending claim 1 to recite the sequence of the 50-100 fragment, or refer to a sequence identification number, to clarify that the sequence used in the presently claimed method is not mutated as per the prior art.

Upon review of the specification, it appears that the specification does not depict the sequence, nor does the specification contain a sequence listing. However, the specification makes it clear that the sequence used for the experiments was amino acids 50-100 of the normal, human, ATF2 sequence, which was known in the art since 1989 (see attached printout from GenBank; accession number NP_008171). Accordingly, those skilled in the art would immediately recognize the sequence 50-100 of ATF2.

Amendments to the Specification

Applicants respectfully ask the Examiner to enter the amendments to the specification starting on page 3 of this document. Except for the deletion of "(nciarray.nci.nih.gov)" in the paragraph at page 63, lines 20-28 deleting a reference to a hyperlink at the request of the Examiner, all of the proposed Amendments to the Specification are made to demarcate trademarks

correctly at the request of the Examiner. Paragraphs at page 39, lines 9-16; page 40, lines 7-19; page 52, line 29 to page 53, line 7; page 59, lines 15-25; and page 63, lines 20-28 are also amended in the unentered Amendments to the Specification filed March 21, 2005. These paragraphs in the present Amendment show both the changes filed March 21, 2005 and new proposed changes. No new matter has been added by way of these proposed amendments.

Please note that trademarks have been added to company names if those names were designated as trademarks according to the U.S.P.T.O as indicated in

http://www.uspto.gov/web/menu/search.html

Other company names that are not trademarked according to the U.S.P.T.O database were not amended.

Claim Status

Claims 1, 3, 4, and 6-44 are currently pending. Claim 2 is canceled and claims 16-19, 22, and 30-32 are withdrawn. Claims 1, 3, 4, 6-15, 20, 21, 23-29, and 33-44 are currently under examination.

It is propose to amend independent claims 1 and 13 by adding the limitations of dependent claims 3 and 14, respectively, and by specifying that the inhibitory N-terminal fragment of ATF2 comprises amino acid residues from about residue 50 to about residue 100.

It is also proposed to cancel claims 3, 6, 7, 14, 33, 34, and 44.

It is also proposed to amend claim 4 to recite that the fragment *consists essentially of* amino acid residues from about residue 50 to about residue 75 of ATF2. Claim 4 is also to be amended to depend on claim 1, following cancellation of claim 3.

It is also proposed to amend claims 12 and 29 to recite that the ATF2 inhibitory peptide *sensitizes* the tumor cells to subsequent radiation treatment.

It is further proposed to amend claim 35 to depend from claim 1 instead of claim 34, and to recite language that the Examiner proposed on pages 22 (section 22) and 24 (section 24) of the Office Action. The proposed language on page 22 of the Office Action corrects an obvious typographical error by replacing "increase" with "increases." Support for the proposed language found on page 24 of the Office Action can be found on page 60, line 28 to page 61, line 2 of the specification as filed.

New claims 47-49 are also proposed.

Election/Restriction

Applicants thank the Examiner for rejoining claims 6 and 7 with the other claims drawn to the elected invention and for examining claims 6 and 7.

Response to Amendment

The Examiner asserts that the Amendment filed March 21, 2005 is non-compliant because the amended paragraphs do not include markings showing the changes that have been made relative to the immediate prior versions. A Notice of Non-Compliant Amendment for the Amendment filed March 21, 2005 has been included with the pending Office Action. Applicants are required to re-submit the corrected section of the non-compliant Amendment for the Amendment to be compliant according to the Examiner. The Examiner has not entered the Amendments to the Specification filed March 21, 2005.

Applicants thank the Examiner for examining this application before Applicants have addressed the issues in the Notice of Non-Compliant Amendment. Applicants include herewith a corrected version of the "Amendments to the Specification" filed March 21, 2005 (annexed as Exhibit 1) with markings in response to the Notice. Applicants also have corrected the page and line numbers corresponding to each corrected paragraph in the submitted corrected version. Entry of the corrected version is respectfully requested.

Objections to the Specification

The Examiner has maintained his objection to the specification because the specification refers to hyperlinks. Applicants have requested that references to hyperlinks be deleted in the specification at page 63, line 23 and at page 64, line 1 as shown in the corrected "Amendments to the Specification" (see Exhibit 1). Applicants respectfully request entry of corrected "Amendments to the Specification" be entered and removal of this objection as moot.

The Examiner has maintained his objection to the specification because the specification uses improperly demarcated trademarks. Applicants have requested that the specification be amended to demarcate trademarks properly both in the corrected "Amendments to the Specification" and as part of this Amendment. Entry of this amendment and removal of this objection is respectfully requested.

The Examiner has maintained his objection to the specification because "Clontech" is misspelled. Applicants have requested that "Clonetech" be replaced with "Clontech" as shown in the corrected "Amendments to the Specification." Applicants respectfully ask that this amendment be entered and that this objection be removed.

Claim Rejection -- 35 U.S.C. §112

The Examiner has maintained his rejection of claims 1, 8-13, 15, 20, 21, 23-29, and 33 under 35 U.S.C. §112, first paragraph for failing to comply with the written description requirement. According to the Examiner, the specification does not sufficiently support the recitation of the genus, "inhibitory N-terminal fragment of ATF2," in the claims. The Examiner asserts that "the description of 4 N-terminal fragments of ATF2, not all of which inhibit the

activity of ATF2, is not representative or adequately descriptive of the genus of fragments of ATF2 to which the claims are directed" (see page 7 of the Office Action). The Examiner further contends that the genus of substances defined by its functional properties as set forth in the claims does not provide adequate written description of the genus.

To overcome this rejection, claim 1 is amended to recite that the inhibitory N-terminal fragment of ATF2 comprises amino acid residues from about residue 50 to about residue 100. Claim 13 is amended to recite polypeptide comprising an inhibitory ATF2 N-terminal fragment consisting essentially of from about residue 50 to about residue 100. These proposed amendments add a structural limitation (in addition to the already present functional limitation) to the genus recited in these claims and, thus, provide adequate written description. It is noted that the amendments to claims 1 and 13 include the limitations of proposed canceled claims 3 and 14, respectively, which were not part of this written description rejection.

Withdrawal of this rejection is respectfully requested.

Claim Rejection - 35 U.S.C §102

The Examiner maintains that claims 1, 3, 4, 6-10, 12-14, 20, 23-26, 29, 33-39, 43, and 44 are anticipated by U.S. Patent No. 6,579,856 (the '856 patent) , as *evidenced* by van Dam *et al.* (EMBO J. 1995; 14: 1798-1811; "van Dam"), and as *evidenced* by Bhoumik *et al.* (Proc. Natl. Acad. Sci. USA. 2004;101;4222-4227; "Bhoumik"). The Examiner asserts that the dominant negative ATF2 disclosed in the '856 patent and as explained in van Dam is equivalent to the ATF2 inhibitor peptide presently claimed. According to the Examiner, van Dam teaches a dominant negative mutant of ATF2 comprising the minimal transactivation domain at the amino-terminus of ATF2 comprising amino acid 19-96.

This rejection is respectfully traversed. First, the '856 patent discloses a dominant negative ATF2 (see column 12, lines 17-21), but does not disclose *inhibitory* ATF2 fragments comprising amino acid residues from about 50 to about 100 of ATF2 as set forth in the proposed

claims. Instead, the '856 patent cites the van Dam article as describing the dominant negative ATF2. The Examiner contends that the citation in the '856 to the van Dam reference is evidence of anticipation, since van Dam allegedly discloses dominant negative ATF2 fragments comprising amino acid residues from about 50 to about 100.

Applicants traverse this rejection. The alleged "dominant negative" in van Dam being referenced in the '856 patent refers to the *mutant* ATF2 fragments, i.e., those that differ in structure and function from the wild-type ATF2 . See, *e.g.*, Figure 4A of van Dam which demonstrates that an ATF2 fragment having a *mutation* in amino acids 69 and/or 71 is unable to become phosphorylated by SAPK and transactivate gene expression in response to UV.[1] This was discussed during the interview.

Claims 1 and 13 have been amended to recite that the N-terminal inhibitory fragment is a fragment of the *wild-type* ATF2, to clarify that this fragment is not mutated at residues 69 and 71 as taught in the '856 patent and van Dam. This is supported by the specification at page 51:

> Peptide II harbors amino acid residues 50-100 of the ATF2 cDNA, which contains the phosphorylation sites for the stress kinases p38 and JNK.

The phosphorylation sites referred to are residues 69 and 71, as evidenced by the disclosure on page 41:

> Among important sites within the first 200 amino acids are the phosphoacceptor sites for p38 and JNK (amino acid residues 69 and 71) (Gupta et al., Science 1995; 267:389-393) and the region required for ATF2 intra-molecular inhibition (within amino acid residues 150-200) (Fuchs, S.Y., et al., Mol. Cell Biol. 1999; 19:3289-3298).

Moreover, at page 40, lines 4-7, the specification explicitly states that

[1] This is arguably not even a "dominant negative," in the conventional sense since van Dam's experiments using a reporter gene preclude any evaluation of the effects of any wild-type ATF2 that may be expressed by the cells-since endogenous ATF2 lacks the requisite GAL4 binding domain required for reporter gene activation..

> Oligonucleotides corresponding to ATF2 peptides within amino acid residue 1-50 (peptide I), 50-100 (peptide II), 100-150 (peptide III) and 150-200 (peptide IV) were PCR amplified and cloned into *Bam*HI and *Xba*I sites of pcDNA3 (Invitrogen, Carlsbad, CA), which contains HA-penetratin tag on its NH2-terminal domain.

Accordingly, the specification makes it clear that the fragments used in the claimed methods are derived from non-mutated or non-variant, i.e., *wild-type*, ATF2.

The only other ATF2 fragments besides the mutated ATF2 disclosed in van Dam are wild-type ATF2 fragments containing amino acids 19-96 or 1-112 linked to a Gal4-binding protein. van Dam discloses that these fragments become phosphorylated by a SAPK in response in response to UV induced stress and are then able to transactivate a reporter gene expression in HeLa, F9 and other cells. However, this observation is irrelevant to the presently claimed method, and certainly does not anticipate the present claims.

The present claims call for a method of inhibiting tumor cell growth using an inhibitory ATF2 peptide comprising amino acid residues from about 50 about 100. The Examiner contends that the non-mutated ATF2 regions disclosed in van Dam would inherently inhibit tumor cell growth, since the 1-112 fragment *comprises* the amino acid fragment of ATF2 residues 50-100, and since the 19-96 fragment almost comprises this fragment.

To the contrary, van Dam is *prima facie* evidence that these fragments do not inhibit the growth of tumor cells, otherwise the HeLa cells (carcinoma) and F9 cells (embryonic carcinoma) used by van Dam could not have been cultivated and used for van Dam's experiments, since they would be inhibited by the introduction of the 1-112 and/or 19-96 fragment. This is clearly not the case. Thus, contrary to the present claims, van Dam does not demonstrate that the 19-96 or 1-112 ATF2 fragment has any inhibitory activity in tumor cells, and he certainly does not disclose that a fragment of about 50-100 would inhibit the growth of tumor cells.

Moreover, as has been previously argued, an inhibitory peptide comprising a fragment of from **about** residue 50 to **about** residue 100 of ATF2 does not encompass a significantly larger fragment of 1-112 or 19-96 as disclosed in van Dam. Neither the '856 patent's disclosure of dominant-negative (i.e., mutated) ATF2, nor van Dam's disclosure of the non-inhibitory 19-96 or 1-112 fragments of ATF2, anticipate this claimed fragment, much less anticipate its use to inhibit tumor cell growth.

In view of the foregoing, neither the '856 alone or as evidenced by van Dam disclose the subject matter of the present claims which is directed to inhibiting tumor cell growth. Withdrawal of this rejection is respectfully requested.

Referencing claims 35-39, 43, and 44, the Examiner also contends that, although the prior art does not teach the subject matter recited in these claims, Bhoumik demonstrates that these claim recitations are inherent properties of the referenced prior art and, therefore, anticipated.

As demonstrated *supra*, the prior art does not disclose ATF2 fragments comprising residues from about 50 to about 100 which *inhibit* the growth of tumor cells, and do not anticipate the present claims. Hence, without anticipation, there can be no inherent anticipation. Applicants respectfully request the removal of this rejection.

Claim Rejection #1 Under 35 U.S.C. §103-Obviousness

Claims 1, 10, 11, 23, 26-28, 40, and 41 stand rejected as obvious over the '856 patent, as evidenced by the van Dam article, in view of Ivanov *et al.* (*Oncogene.* 2000; 19: 3003-12; "Ivanov"). According to the Examiner, the '856 patent, as evidenced by van Dam, makes it obvious to use an inhibitory N-terminal fragment to treat a tumor or to inhibit or sensitize tumor cells as set forth in the present claims. The Examiner further contends that while the '856 patent does not teach using an ATF2 inhibitor in combination with the p38 inhibitor, SB203580, Ivanov teaches that SB203580 sensitizes tumors to UV-induced apoptosis.

A finding of *prima facie* obviousness requires that the combined references teach or suggest all of the claim limitations. As discussed for the anticipation rejection *supra*, the '856 patent, as evidenced by van Dam, does not teach the inhibitory N-terminal fragment of ATF2 (50-100) of the present claims, and only teaches an inhibitory ATF2 peptide that is *mutated* at phosphorylation sites. Nor does van Dam suggest a method of inhibiting or sensitizing tumor cells using an ATF fragment of about 50-100 (since it is not disclosed), or any other ATF2 fragment. Further, the '856 patent, as evidenced by van Dam, also fails to teach or suggest this fragment since it only refers to van Dam's mutated ATF2 fragment (i.e., the alleged dominant negative).

Finally, Ivanov does not remedy the deficient teachings in the '856 patent or van Dam and does not disclose or suggest the inhibitory ATF2 fragment presently claimed. Therefore, Ivanov cannot be combined with the '856 patent or van Dam to arrive at the presently claimed invention.

Thus, Applicants traverse this rejection because neither the '856 patent, as evidenced by van Dam, nor Ivanov teaches or suggests the inhibitory N-terminal fragment as recited in the claims, as such, combination of these references also cannot disclose the claimed fragment. Applicants respectfully request withdrawal of this rejection.

Claim Rejection #2 Under 35 U.S.C. §103-Obviousness

The Examiner has maintained his rejection of claims 13, 15, 21, 23-26, and 29 as obvious over the '856 patent, as evidenced by van Dam, in view of U.S. Patent No. 6,335,178 (the '178 patent). According to the Examiner, the '856 patent, as evidenced by van Dam, renders obvious an inhibitory N-terminal fragment of 50-100 and methods using the same. The Examiner asserts that the '178 patent teaches methods for facilitating the production of recombinant proteins in host cells by fusing the polynucleotide sequence encoding a protein to the polynucleotide sequence encoding the amino acid sequence of a translocation signal sequence. Thus, according to the

Examiner, it would have been *prima facie* obvious to produce a dominant negative mutant of ATF2 according to the '856 patent by the methodology described by the '178 patent.

This rejection is respectfully traversed. First, as explained above and as discussed during the interview, the present "dominant negative" mutation referenced in the '856 patent is the *mutated* ATF2 fragment taught by van Dam. For the above reasons, this is completely distinct from the non-mutated ATF2 fragment used in the claimed method.

Moreover, even improper combination of the references do not teach or suggest all of the present claim limitations. As discussed in the "Claim Rejection #1 Under 35 U.S.C. §103-Obviousness" section *supra*, the '856 patent, as evidenced by van Dam, does not teach or suggest the inhibitory ATF2 fragment of amino acid residues from about 50 to about 100 as presently claimed. The '178 patent also does not teach or suggest the inhibitory ATF2 fragment as claimed, much less its use for inhibiting or sensitizing tumor cell growth.

Withdrawal of this rejection is respectfully requested.

Claim Rejection #3 Under 35 U.S.C. §103-Obviousness

The Examiner has maintained his rejection of claims 27 and 28 as obvious over the '856 patent, as evidenced by van Dam, in view of the '178 patent and in further view of Ivanov. According to the Examiner, it would have been *prima facie* obvious to have treated tumors by a process comprising using a polypeptide comprising a dominant negative mutant of ATF2 according to the '856 patent and a translocation signal sequence according to the '178 patent and further treating the tumor by administering an effective dose of SB203580 to sensitize the tumor cells to UV-irradiation as taught by Ivanov.

Applicants traverse this rejection because the combined references do not teach or suggest all of the claim limitations. As discussed in the "Claim Rejection #1 Under 35 U.S.C. §103-Obviousness" and "Claim Rejection #2 Under 35 U.S.C. §103-Obviousness" sections *supra*, none

of the prior art documents referenced by the Examiner teaches or suggests the inhibitory ATF2 fragment of amino acid residues from about 50 to about 100 of the proposed claims.

As such, withdrawal of this rejection is believed to be in order.

New Grounds of Objection

The Examiner has objected to claim 1 because the listing of agents in the claims uses the connector "or" rather than "and." This objection has been rendered moot in light of the amended claim 1.

The Examiner has objected to claim 4 for being improperly dependent form for failing to further limit the subject matter of the previous claim and for being a substantial duplicate of claim 3. By this amendment, Claim 4 has been amended to recite consisting essentially of a smaller fragment. Accordingly, withdrawal of this rejection is respectfully requested.

The Examiner has objected to claims 1, 3, 4, and 6-12 for being drawn in the alternative to the subject matter of the non-elected invention. This objection have been rendered moot by the proposed amendment to claim 1 limiting this claim to a precise inhibitory N-terminal fragment of ATF2.

The Examiner has objected to claim 35 because "increases" was mistyped as "increase." Applicants have amended claim 35 to replace "increase" with "increases."

In light of the above amendments and remarks, Applicants respectfully ask for the removal of the above new objections.

New Grounds of Rejection

The Examiner has rejected claims 1, 3, 4, 6-12, and 34-44 under 35 U.S.C. §112, second paragraph as being indefinite. According to the Examiner, the phrase "the ATF2 N-terminal antagonist fragment" in claim 1 is indefinite This rejection has been rendered moot by the proposed deletion of this phrase from the claim 1.

The Examiner asserts that claim 4 is indefinite because it sets forth the phrase "the inhibitory N-terminal fragment of ATF2 comprises amino acid residues from about residue 50 of ATF2 to about 75 of ATF2." This rejection has been rendered moot by the proposed amendment to claim 4.

The Examiner asserts that claims 34-44 are indefinite because claim 34 depends from itself and is a method claim, but does not recite an active step. This rejection is rendered moot by cancellation of claims 34 and 44.

The Examiner asserts that claims 35-44 are indefinite because it is unclear to what standard or extent the claimed fragment "further increase[s] the activity of a c-jun family member" as recited in claim 35. By this amendment, this phrase is replaced with the phrase suggested by the Examiner on page 24 of the Office Action. This phrase indicates a baseline to determine an increase in the activity of a c-jun family member and, thus, proposed claim 35 is not indefinite.

The Examiner asserts that claims 37-44 are indefinite because the term "the tumor cell" lacks antecedent basis. Applicants have amended claim 35 (from which claims 37-43 depend) to depend from claim 1 which recites "a tumor cell" and, thus, antecedent basis would be present should the proposed claims be entered.

The Examiner asserts that claim 44 is indefinite because it is unclear to what standard or extent the claimed fragment further inhibits the metastasis of melanoma cells. By this amendment, claim 44 is canceled. The subject matter of claim 44 is now present in new independent claim 45.

Claims 1, 3, 4, and 6-12 are rejected under 35 U.S.C. §112, first paragraph for introducing new matter because the specification does not support a method for inhibiting the growth of tumor cells or treating cancer comprising inhibiting transcriptional activity of ATF2 by contacting the cells with an **agent** consisting of at least one of any of the non-traditional therapeutic modalities recited in the claims. The Examiner states that the specification would provide the necessary support if claim 1 was amended to recited that the cells were contacted with a "pharmaceutical composition comprising an agent."

Applicants thank the Examiner for his suggestion but instead have amended claim 1 to recite that the tumor cell is contacted by an inhibitory N-terminal fragment of ATF2 comprising residues about 50-100. It is respectfully submitted that insertion of the term "pharmaceutical composition" into claim 1 would imply that the claim is limited to *in vivo* contacting, since pharmaceutical compositions are not used when contacting cells *in vitro*.

The Examiner is respectfully requested to remove the above new rejections in light of the amendments and arguments set forth above. .

Conclusion

In view of the above amendments and remarks, it is respectfully requested that the application be reconsidered, that the proposed amendment be entered, and that all pending claims be allowed and the case passed to issue. Since the amendments address the Examiner's rejections and would place the claims in condition for allowance, or at least in better form for consideration on appeal, entry is proper. If there are any other issues remaining which the Examiner believes could be resolved through a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Dated: December 9, 2005

Respectfully submitted,

By _____

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1: NP_001871. Reports activating transc...[gi:22538422]

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LOCUS       NP_001871                 505 aa            linear   PRI 06-NOV-2005
DEFINITION  activating transcription factor 2 [Homo sapiens].
ACCESSION   NP_001871
VERSION     NP_001871.2  GI:22538422
DBSOURCE    REFSEQ: accession NM_001880.2
KEYWORDS    .
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Euarchontoglires; Primates; Catarrhini;
            Hominidae; Homo.
REFERENCE   1  (residues 1 to 505)
  AUTHORS   Bhoumik,A., Takahashi,S., Breitweiser,W., Shiloh,Y., Jones,N. and
            Ronai,Z.
  TITLE     ATM-dependent phosphorylation of ATF2 is required for the DNA
            damage response
  JOURNAL   Mol. Cell 18 (5), 577-587 (2005)
   PUBMED   15916964
  REMARK    GeneRIF: Data demonstrate that the protein kinase ATM
            phosphorylates ATF2 on serines 490 and 498 following ionizing
            radiation (IR).
REFERENCE   2  (residues 1 to 505)
  AUTHORS   Bailey,J. and Europe-Finner,G.N.
  TITLE     Identification of human myometrial target genes of the c-Jun
            NH2-terminal kinase (JNK) pathway: the role of activating
            transcription factor 2 (ATF2) and a novel spliced isoform
            ATF2-small
  JOURNAL   J. Mol. Endocrinol. 34 (1), 19-35 (2005)
   PUBMED   15691875
  REMARK    GeneRIF: genes affected by ATF2 and ATF2-sm appear to belong to
            discrete groups
REFERENCE   3  (residues 1 to 505)
  AUTHORS   Pearson,A.G., Curtis,M.A., Waldvogel,H.J., Faull,R.L. and
            Dragunow,M.
  TITLE     Activating transcription factor 2 expression in the adult human
            brain: association with both neurodegeneration and neurogenesis
  JOURNAL   Neuroscience 133 (2), 437-451 (2005)
   PUBMED   15878807
  REMARK    GeneRIF: ATF2 expression in the neuron of normal human brain. But
            downregulation in the Neurodegenerative Disease( Alzheimer disease,
            Huntington disease and Parkinson disease).
REFERENCE   4  (residues 1 to 505)
  AUTHORS   Beausoleil,S.A., Jedrychowski,M., Schwartz,D., Elias,J.E.,
            Villen,J., Li,J., Cohn,M.A., Cantley,L.C. and Gygi,S.P.
  TITLE     Large-scale characterization of HeLa cell nuclear phosphoproteins
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JOURNAL Proc. Natl. Acad. Sci. U.S.A. 101 (33), 12130-12135 (2004)
PUBMED 15302935
REFERENCE 5 (sites)
AUTHORS Beausoleil,S.A., Jedrychowski,M., Schwartz,D., Elias,J.E., Villen,J., Li,J., Cohn,M.A., Cantley,L.C. and Gygi,S.P.
TITLE Large-scale characterization of HeLa cell nuclear phosphoproteins
JOURNAL Proc Natl Acad Sci U S A 101 (33), 12130-12135 (2004)
PUBMED 15302935
REFERENCE 6 (residues 1 to 505)
AUTHORS Kravets,A., Hu,Z., Miralem,T., Torno,M.D. and Maines,M.D.
TITLE Biliverdin reductase, a novel regulator for induction of activating transcription factor-2 and heme oxygenase-1
JOURNAL J. Biol. Chem. 279 (19), 19916-19923 (2004)
PUBMED 14988408
REMARK GeneRIF: ATF2 and HO-1 are regulated and induced by biliverdin reductase
REFERENCE 7 (residues 1 to 505)
AUTHORS Hong,S., Choi,H.M., Park,M.J., Kim,Y.H., Choi,Y.H., Kim,H.H., Choi,Y.H. and Cheong,J.
TITLE Activation and interaction of ATF2 with the coactivator ASC-2 are responsive for granulocytic differentiation by retinoic acid
JOURNAL J. Biol. Chem. 279 (17), 16996-17003 (2004)
PUBMED 14734562
REMARK GeneRIF: differentiation-dependent expression and phosphorylation of ATF2 protein physically and functionally interacts with C/EBPalpha and coativator ASC-2 and synergizes to induce target gene transcription during granulocytic differentiation
REFERENCE 8 (residues 1 to 505)
AUTHORS Averous,J., Bruhat,A., Jousse,C., Carraro,V., Thiel,G. and Fafournoux,P.
TITLE Induction of CHOP expression by amino acid limitation requires both ATF4 expression and ATF2 phosphorylation
JOURNAL J. Biol. Chem. 279 (7), 5288-5297 (2004)
PUBMED 14630918
REMARK GeneRIF: ATF4 and ATF2 have roles in regulating CHOP expression
REFERENCE 9 (residues 1 to 505)
AUTHORS Berger,A.J., Kluger,H.M., Li,N., Kielhorn,E., Halaban,R., Ronai,Z. and Rimm,D.L.
TITLE Subcellular localization of activating transcription factor 2 in melanoma specimens predicts patient survival
JOURNAL Cancer Res. 63 (23), 8103-8107 (2003)
PUBMED 14678960
REMARK GeneRIF: In melanoma strong cytoplasmic ATF2 expression was associated with primary specimens rather than metastases and with better survival. Strong nuclear ATF2 expression was associated with metastatic specimens and with poor survival.
REFERENCE 10 (residues 1 to 505)
AUTHORS Ho,D.T., Bardwell,A.J., Abdollahi,M. and Bardwell,L.
TITLE A docking site in MKK4 mediates high affinity binding to JNK MAPKs and competes with similar docking sites in JNK substrates
JOURNAL J. Biol. Chem. 278 (35), 32662-32672 (2003)
PUBMED 12788955
REFERENCE 11 (sites)
AUTHORS Ho,D.T., Bardwell,A.J., Abdollahi,M. and Bardwell,L.
TITLE A docking site in MKK4 mediates high affinity binding to JNK MAPKs and competes with similar docking sites in JNK substrates
JOURNAL J Biol Chem 278 (35), 32662-32672 (2003)
PUBMED 12788955
REFERENCE 12 (residues 1 to 505)
AUTHORS Kool,J., Hamdi,M., Cornelissen-Steijger,P., van der Eb,A.J.,

Terleth,C. and van Dam,H.
TITLE Induction of ATF3 by ionizing radiation is mediated via a signaling pathway that includes ATM, Nibrin1, stress-induced MAPkinases and ATF-2
JOURNAL Oncogene 22 (27), 4235-4242 (2003)
PUBMED 12833146
REMARK GeneRIF: ATF-2 and ATF3 seem to play an important role in the protective response of human cells to ionizing radiation
REFERENCE 13 (residues 1 to 505)
AUTHORS Hayakawa,J., Depatie,C., Ohmichi,M. and Mercola,D.
TITLE The activation of c-Jun NH2-terminal kinase (JNK) by DNA-damaging agents serves to promote drug resistance via activating transcription factor 2 (ATF2)-dependent enhanced DNA repair
JOURNAL J. Biol. Chem. 278 (23), 20582-20592 (2003)
PUBMED 12663670
REMARK GeneRIF: JNK-dependent phosphorylation of ATF2 plays an important role in the drug resistance phenotype likely by mediating enhanced DNA repair by a p53-independent mechanism.
REFERENCE 14 (residues 1 to 505)
AUTHORS Wen-Sheng,W.
TITLE ERK signaling pathway is involved in p15INK4b/p16INK4a expression and HepG2 growth inhibition triggered by TPA and Saikosaponin a
JOURNAL Oncogene 22 (7), 955-963 (2003)
PUBMED 12592382
REMARK GeneRIF: Phosphorylation of one of the downstream transcriptional factors of MAPK cascade, ATF2, was 3.2- and 2.0-fold induced by TPA and Saikosaponin a, respectively.
REFERENCE 15 (residues 1 to 505)
AUTHORS Ouwens,D.M., de Ruiter,N.D., van der Zon,G.C., Carter,A.P., Schouten,J., van der Burgt,C., Kooistra,K., Bos,J.L., Maassen,J.A. and van Dam,H.
TITLE Growth factors can activate ATF2 via a two-step mechanism: phosphorylation of Thr71 through the Ras-MEK-ERK pathway and of Thr69 through RalGDS-Src-p38
JOURNAL EMBO J. 21 (14), 3782-3793 (2002)
PUBMED 12110590
REMARK GeneRIF: activation by growth factors via phosphorylation of Thr71 through the Ras-MEK-ERK pathway and of Thr69 through RalGDS-Src-p38
REFERENCE 16 (sites)
AUTHORS Ouwens,D.M., de Ruiter,N.D., van der Zon,G.C., Carter,A.P., Schouten,J., van der Burgt,C., Kooistra,K., Bos,J.L., Maassen,J.A. and van Dam,H.
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AUTHORS Ban,N., Yamada,Y., Someya,Y., Ihara,Y., Adachi,T., Kubota,A., Watanabe,R., Kuroe,A., Inada,A., Miyawaki,K., Sunaga,Y., Shen,Z.P., Iwakura,T., Tsukiyama,K., Toyokuni,S., Tsuda,K. and Seino,Y.
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PUBMED 602896
REFERENCE 52 (sites)
AUTHORS Denys,H., Desmet,R., Stragier,M., Vergison,R. and Lemahieu,S.F.
TITLE Cystitis emphysematosa
JOURNAL Acta Urol Belg 45 (4), 327-331 (1977)
PUBMED 602896
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On Aug 29, 2002 this sequence version replaced gi:4503033.

Summary: This gene encodes a transcription factor that is a member of the leucine zipper family of DNA binding proteins. This protein binds to the cAMP-responsive element (CRE), an octameric palindrome. The protein forms a homodimer or heterodimer with c-Jun and stimulates CRE-dependent transcription. The protein is also a

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            histone acetyltransferase (HAT) that specifically acetylates
            histones H2B and H4 in vitro; thus it may represent a class of
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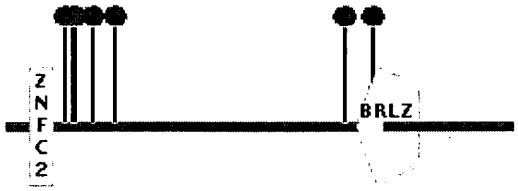
Dec 1 2005 15:15:38

Human Protein Reference Database

Activating transcription factor 2

Molecular Class	Transcription factor
Molecular Function	Transcription factor activity
Biological Process	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism



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